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Pharmacy Benefits Management
Strategic Healthcare Group
and the Medical Advisory Panel

The Pharmacologic Management of Cognitive Changes in Alzheimer's Disease

The Pharmacological Management of Cognitive Changes in Alzheimer's Disease has undergone thorough review by generalist as well as specialists in the field. It is currently awaiting concurrence from the National Advisory Council for Adoption, Development and implementation of Clinical Practices Guidelines. Due to the time-sensitive nature of the information contained therein, it is posted here for your use until its distribution under the official cover.

Department of Veterans Affairs
Veterans Health Administration
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Department of Veterans Affairs

Memorandum

Date: August 15, 1999

From: Acting Under Secretary for Health (10)

Subj: The Pharmacologic Management of Cognitive Changes in Alzheimer's Disease

To: VISN Directors, VISN Clinical Managers, Medical Center Directors, Chiefs of Staff and Patient Care Staffs

1. To date, VHA has approved nine Pharmacologic Management Algorithms or Guidelines for the most common diseases associated with the veteran patient population (these documents may be referenced at *http://www.dppm.med.va.gov*), while three additional Pharmacologic Management Algorithms and one Clinical Practice Guideline are being reviewed for approval.

2. Please find the attached drug treatment guidelines entitled *The **Pharmacologic Management of Cognitive Changes in Alzheimer's Disease***. The Cognitive Changes in Alzheimer's Disease Ad Hoc Committee and the Medical Advisory Panel of VHA's Pharmacy Benefits Management Strategic Healthcare Group facilitated and coordinated this effort. These guidelines, previous guidelines, and those to follow are intended to promote consistent, quality patient care for patients throughout the VA health care system.

3. The guidelines are based on nationally recognized treatment guidelines, current literature and expert opinion from clinicians across the VA system. The guidelines are dynamic and will be revised, as new clinical data become available. Also, the guidelines are not intended to interfere with clinical judgement that might dictate alternative therapies under special circumstances. Rather, they are intended to assist practitioners in providing consistent, high quality care.

4. I commend the efforts put forth in the development of these guidelines and know from the many comments received from throughout the VA that they are a welcome tool for practitioners. I strongly encourage their utilization and will closely follow their implementation, as well as the outcomes associated with their use. They constitute a significant advancement in VHA's evolution toward a truly integrated health care delivery system.

Thomas L. Garthwaite, M.D.

Attachment

THE PHARMACOLOGIC MANAGEMENT OF COGNITIVE CHANGES IN ALZHEIMER'S DISEASE

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The mission of the Cognitive Changes in Alzheimer's Disease Ad Hoc Committee for the Pharmacy Benefits Management (PBM) Strategic Healthcare Group includes the development of evidence-based pharmacologic management guidelines for improving quality and providing best-value patient care.

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The mission of the Medical Advisory Panel (MAP) for Pharmacy Benefits Management (PBM) includes the development of evidence-based pharmacologic management guidelines for improving quality and providing best-value patient care.

The MAP is comprised of practicing VA and Department of Defense physicians from facilities across the nation:

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Pharmacy Benefits Management (PBM) Strategic Healthcare Group (SHG)

VHA's PBM SHG has been directed by the Under Secretary for Health to coordinate the development of guidelines for the pharmacologic management of common diseases treated within the VA, establish a national level VA formulary, and to manage pharmaceutical costs, utilization, and measure outcomes as they apply to patient care. The MAP provides support and direction to the PBM staff, located in Washington DC and Hines, Illinois.

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Development of the Guidelines

Whenever possible, the PBM and MAP rely on evidence-based, multidisciplinary, nationally recognized consensus statements for the basis of VA guidelines. Draft guidelines are sent to the field for comments prior to being finalized, so that special consideration is given to the needs of the VA population.

The diagnosis of Alzheimer's disease (AD) is discussed in the guidelines, "Dementia Identification and Assessment: Guidelines for Primary Care Practitioners" (U.S. Department of Veterans Affairs/University Health System Consortium, 1997).

Use of the Guidelines

The purpose of the guidelines is to assist practitioners in treating the cognitive symptoms of mild to moderate AD. These guidelines were developed to meet the needs of primary care providers, but they will also be useful for geriatricians, neurologists, and psychiatrists. The guidelines will serve as a basis for monitoring local, regional, and national patterns of pharmacologic care.

These guidelines do not include all methods of care, so references will be made to various nonpharmacologic methods of management. Ultimately, the definition of best care must rely on the clinician's judgement for what would work best for an individual patient. The pharmacologic management of AD is a small segment of a larger care plan that includes social and behavioral approaches as well.

Updating the Guidelines

PBM will review the guidelines routinely. Updating will occur as new information is made available from well-designed, scientifically valid studies and as outcome data may direct.

A current copy of the pharmacologic management guidelines can be obtained from the Pharmacy Benefits Management home page at http://www.dppm.med.va.gov

Referencing the Guidelines

These guidelines should be referenced as: Pharmacy Benefits Management-Medical Advisory Panel. The Pharmacologic Management of Cognitive Changes in Alzheimer's Disease. VHA PBM-SHG Publication No. 99-0013. Hines, IL: Pharmacy Benefits Management Strategic Healthcare Group, Veterans Health Administration, Department of Veterans Affairs. August 1999.

Acknowledgments*

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* *This list does not represent all the clinicians who reviewed the guidelines, rather those who wished to be acknowledged. The Pharmacy Benefits Management and Medical Advisory Panel take full responsibility for the content of these guidelines.*

EXECUTIVE SUMMARY

1. Treatment of Alzheimer's disease (AD) should include concerns about quality of life for the patient and for members of his/her family. Therefore, it is important to respect patient and family preferences when making treatment recommendations.

2. The clinical diagnosis of AD can be made using the criteria of the Diagnostic and Statistical Manual – IV (American Psychiatric Association, 1994), as outlined in the VA Donepezil Reporting Form (Appendix I). An algorithm guiding the differential diagnosis of dementia is presented in Appendix II.

3. Once the diagnosis of AD has been made, the severity of the dementia can be estimated and monitored using a cognitive instrument such as the Mini-Mental State Examination (MMSE) (Appendix III). Mild to moderate AD patients usually score 10 or above on the MMSE.

4. There is a cholinergic deficit in brains of AD patients, explaining why cholinesterase inhibitors may produce modest improvements in cognitive symptoms of mild to moderate AD. Of the currently available agents, donepezil is safer, more selective, and dosed less frequently than tacrine.

5. Primary care providers and specialists who have prescribing authority for donepezil and other drugs in this class should follow the inclusion and exclusion criteria outlined in the VA Donepezil Reporting Form (Appendix I).

6. Cholinesterase inhibitors are not recommended for AD patients who have severe dementia (<10 on MMSE) or certain medical conditions such as serious liver disease, active alcoholism, active peptic ulcer disease, severe COPD/asthma, bradycardia ≤ 50 beats/minute, or significant parkinsonism.

7. Certain medications, such as those with anticholinergic activity (see Appendix IV), should be limited when a patient is taking donepezil. Another relative contraindication to cholinesterase inhibitors would be the lack of a caregiver to monitor efficacy, adverse effects, and adherence to drug therapy.

8. Before starting donepezil, the patient and family need to be advised about its common adverse effects (nausea, anorexia, diarrhea, bradycardia, dizziness, and agitation). If surgery is planned, the surgeon should be notified about the potential interaction between cholinesterase inhibitors and succinylcholine.

9. The initial dose of donepezil is 5 mg p.o. daily. Follow-up contact should be made in 4-8 weeks to monitor potential adverse effects before increasing the dose to 10 mg p.o. daily.

10. The maintenance dose of donepezil is 5 or 10 mg p.o. daily. A follow-up visit needs to be scheduled 3-4 months after initiating therapy to monitor potential adverse effects and to assess efficacy (improvement may be seen in memory, concentration, language fluency, or word recall). Subsequently, visits can be scheduled at 3-6 month intervals.

11. Cholinesterase inhibitors should be reduced in dosage at any time if the patient develops side effects. They should be discontinued if there is evidence of: a) poor compliance, b) persistent side effects, c) lack of benefit after 6 months, d) mutual agreement between caregiver and provider, e) progression to severe dementia (MMSE <10), or f) development of a serious medical condition.

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I. DEFINITION OF ALZHEIMER'S DISEASE (AD)

All dementing illnesses involve memory impairment in addition to at least one other cognitive abnormality such as aphasia, apraxia, agnosia, or disturbance of executive function. These cognitive impairments must be sufficiently severe to limit social or occupational functioning.

One set of diagnostic criteria for AD, outlined in the VA Donepezil Reporting Form (Appendix I), is from the fourth edition of the Diagnostic and Statistical Manual (DSM IV) of the American Psychiatric Association (1994). The algorithm in Appendix II was developed to guide the clinician in the differential diagnosis of dementia (US Department of Veterans Affairs and University Health System Consortium, 1997).

II. GENERAL PRINCIPLES

A. Alzheimer's disease is the most common dementing illness in North America and Europe, accounting for one-half to two-thirds of all cases of dementia (Wade et al, 1987; Bowler et al, 1998).

B. Symptoms of AD usually begin after the age of 65 years, with the incidence increasing with age (Bachman et al, 1993; van Duijn, 1996). Prevalence figures vary, according to the diagnostic criteria used (Erkinjuntti et al, 1997). Callahan and others (1995) found the prevalence of AD in a primary care practice to vary from 2% (60-65 year olds) to 25.6% (those over 85 years).

C. Besides age, family history of dementia is another risk factor for AD. Early-onset AD may be a dominantly inherited condition associated with a mutation on either chromosome 1, 14, or 21. Late-onset AD appears to vary in prevalence according to the numbers of E4 alleles on the apolipoprotein E (APOE) gene of chromosome 19. At this time, however, APOE genotyping is not sufficiently sensitive or specific to be used routinely as a diagnostic test (Am Coll Med Genetics et al, 1995).

D. The cholinergic hypothesis states that the deficiency of acetylcholine in AD contributes to the cognitive and neuropsychiatric features of the disease (Cummings and Black, 1998; Francis et al, 1999). In theory, drugs that potentiate central cholinergic function should improve cognitive symptoms in early AD.

E. The rules of evidence that were used to develop these clinical recommendations followed the guidelines of Cook and others (1992). Level I evidence exists if data were derived from randomized controlled clinical trials with low false-positive (alpha) errors and low false-negative (beta) errors. Level II evidence is present when data from randomized trials are associated with either high false-positive or high false-negative errors. When the only available data come from randomized concurrent cohort studies, then we have level III evidence.

F. Cholinesterase inhibitors such as tacrine, donepezil, metrifonate and rivastigmine (the latter two are not yet approved for marketing) have been shown in randomized controlled trials (level I evidence) to improve cognitive symptoms in patients with mild to moderate AD (Farlow et al, 1992; Rogers et al, 1996; Cummings et al, 1998; Francis et al, 1999).

G. In one study (level II evidence), chronic use of high doses of tacrine significantly delayed nursing home placement in AD patients, compared to use of low doses (Knopman et al, 1996). In general, AD patients should be living at home and have mild to moderate AD when cholinesterase inhibitors are prescribed (Knopman and Morris, 1997).

III. PATIENT EVALUATION

A. HISTORY

1. The memory disorder of AD is insidious in onset and slowly progressive over years (McKhann et al, 1984). Acute onset of cognitive changes with rapid progression over time is more likely to be associated with delirium or another dementing condition (Clarfield, 1988). An external informant needs to provide the clinician information about the chronology of memory loss and noncognitive symptoms in patients with AD.

2. Other cognitive changes besides memory disorder in early AD include symptoms of parietal lobe dysfunction, such as word-finding problems or geographic disorientation. Frontal lobe dysfunction may also be seen, leading to difficulties in problem-solving, planning, or sequencing multiple tasks over time.

3. Common behavioral changes in early AD include apathy, social withdrawal, irritability, agitation, and dysphoria (Jost and Grossberg, 1996). Significant depression can occur at any stage of the disease, and its recognition requires input from both the patient and the caregiver (Logsdon and Teri, 1995; Lyketsos et al, 1997).

4. Recurrent visual hallucinations or unexplained alterations in consciousness are more likely to be associated with Lewy body dementia than with AD (McKeith et al, 1996). Extrapyramidal signs, such as bradykinesia, rigidity and gait disorder are also seen more commonly in dementia with Lewy bodies than in AD (Hely et al, 1996).

5. The frontotemporal dementias are less common than AD. They are diagnosed clinically, when poor judgement, extreme apathy, executive dysfunction, and disinhibition outweigh the parietal or memory symptoms (Lund and Manchester Groups, 1994).

6. A review of prescription medications and OTC drugs is required in AD patients to check for drugs with anticholinergic activity (Appendix IV). Neuropsychiatric symptoms similar to those seen in AD can be produced by anticholinergic medications and other drugs (Cummings and Black, 1998).

7. The Algorithm Guiding the Differential Diagnosis of Dementia (Appendix II) can help to frame the questions asked in the review of systems.

8. The VA Donepezil Reporting Form (Appendix I) includes a list of medical conditions that are relative contraindications for use of cholinesterase inhibitors.

9. Memory, language, visuospatial, and executive dysfunction in AD usually impair the ability of a patient to perform instrumental activities of daily living (IADLs), such as driving a car, preparing meals, and shopping. The Functional Activities Questionnaire (Appendix V) is a 10-item interview for the caregiver that assesses these disabilities (Pfeffer et al, 1982).

10. As AD progresses, patients lose independence in the ability to perform self-care tasks, such as dressing, bathing, and toileting. The Barthel Index (Appendix VI) is one way to quantitate independence in self-care. Functional scales such as the Barthel are useful in determining the need for support services in patients with AD (Juva et al, 1994).

B. PHYSICAL EXAM / BEHAVIORAL ASSESSMENT

1. The general physical examination should be targeted towards recognition of other treatable dementing illnesses (Appendix II) and medical conditions that may contraindicate use of cholinesterase inhibitors (see VA Donepezil Reporting Form, Appendix I).

2. The neurologic examination should focus on finding signs of other possible dementing illnesses. Appendix II lists conditions with focal signs (tumor, vascular dementia) and extrapyramidal signs (Parkinson's disease, Huntington's disease). Neurologic consultation is warranted when these signs and symptoms are in question.

3. A brief cognitive assessment can be performed with the MMSE of Folstein et al (1975), as outlined in Appendix III. Juva and others (1994) showed that scores of 10-26 on the MMSE correlated with global ratings of mild to moderate dementia on the Clinical Dementia Rating (CDR) of Hughes et al (1982; see Appendix VII). Well-educated patients in early stages of dementia may score higher than 26 on the MMSE (Crum et al, 1993; Katzman et al, 1993).

4. Behavioral changes of AD, such as apathy, irritability, restlessness, depression, and delusions can be assessed with an instrument such as the Neuropsychiatric Inventory (Cummings et al, 1994). If the behaviors are problematic for the patient or caregiver, then psychological or psychiatric consultation is warranted.

5. Tools commonly used to assess dementia patients and caregivers are listed in Appendix 2 of the Dementia Guidelines for Primary Care Practitioners (US Department of Veterans Affairs and University Health System Consortium, 1997).

C. LABORATORY STUDIES

1. Blood work that needs to be ordered in patients with dementia includes complete blood count, serum electrolytes, glucose, creatinine, urinalysis, liver function tests, thyroid stimulating hormone, vitamin B12 level, and syphilis serology (Quality Standards Subcommittee of the American Academy of Neurology, 1994; US Department of Veterans Affairs and University Health System Consortium, 1997).

2. Neuroimaging is usually not necessary if there are clear signs and symptoms of AD for a year or more in a patient over the age of 60 years (Quality Standards Subcommittee of the AAN, 1994). Non-contrast computerized tomography (CT) of the head is indicated if the dementia is abrupt in onset, rapidly-progressive over time, early in onset (less than 60 years of age), associated with atypical features (focal signs, gait disorder, headache, or seizures), or unreliably documented (e.g., absence of an informant).

3. CT is less expensive than MRI, faster to obtain, and less likely to cause claustrophobia. MRI is superior to CT in distinguishing stroke from tumor. Rarely, isodense subdural hematomas are missed by CT, but identified by MRI. Unexplained findings on MRI, such as periventricular white matter changes, should be discussed with a clinical specialist.

4. Neuropsychological evaluation is needed when evaluating demented patients with atypical presentations, when dementia needs to be distinguished from depression, or when the presence of dementia is in doubt (Report of Therapeutics & Technology Assessment Subcommittee of AAN, 1996).

IV. MANAGEMENT OF AD

A. GENERAL

1. Healthcare providers need to educate caregivers about AD and its natural history. There is level I evidence to demonstrate that counseling and social support (day care, home health care, etc) substantially increase the time that AD patients can be managed by spouse-caregivers in the home (Mittleman et al, 1996).

2. Social service or other healthcare providers should discuss financial and legal issues with families of AD patients. This would include signing a healthcare proxy form, assigning power-of-attorney or guardianship, and discussing advanced directives.

3. Caregivers need to know which cognitive symptoms are likely to improve with cholinesterase inhibitors (word recall, concentration, language fluency, and memory). Non-cognitive symptoms of AD, such as apathy, delusions, disinhibition and pacing, have also been shown to improve with tacrine therapy (level II evidence; Kaufer et al, 1996; Raskind et al, 1997).

4. There is level II evidence to show that large savings in the cost of caring for mildly to moderately demented AD patients are achievable with cholinesterase inhibitors (Ernst et al, 1997).

B. CAREGIVER INVOLVEMENT

1. A caregiver of an AD patient must be able to monitor compliance, assess drug efficacy, and report possible adverse effects of donepezil (nausea, anorexia, diarrhea, bradycardia, dizziness, or agitation).

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2. There should be a realistic understanding on the part of the patient and the family that cholinesterase inhibitors may produce only small improvements or no change in the patient's cognitive status (Knopman and Morris, 1997).

3. Caregivers of AD patients often need help with their own physical and emotional problems, so that providers find themselves monitoring two individuals at each office visit.

4. Family members of AD patients may benefit from attending educational classes or support groups at their local VA medical facility or at local chapters of the Alzheimer's Association (1-800-272-3900 or www.alz.org).

C. NON-PHARMACOLOGIC INTERVENTIONS

1. Caregivers need to provide a predictable routine for the patient, so that self-care tasks and meals are on a regular schedule. Limit unexpected visitors, if possible.

2. Advise families to use safety latches to prevent wandering and to get Safe-Return identification bracelets from the Alzheimer's Association (headquarters phone 1-800-272-3900; www.alz.org).

3. Caregivers need to learn the ABCs of behavioral management of AD (Teri, 1997), which involve observing the pattern of cause and effect surrounding unwanted behaviors. Once a pattern is identified, one can break the cycle and change the behavior. For example, the unwanted behavior (B), such as yelling, resisting care, striking, etc., should be recorded (what happened? when? who was present? etc.). The antecedent (A), or trigger (change in daily routine? unexpected visitors? loud noises? etc.), should be identified and removed, if possible. The consequences (C) should also be adjusted as needed, so that more appropriate behaviors are encouraged (through distraction, redirection, etc.) and unwanted behaviors are ignored, to the extent possible.

4. Paranoid and other delusional ideas can often trigger arguments between AD patients and their caregivers. Practitioners need to remind caregivers that "going along" with the patient is usually preferable to an argument. Distressing hallucinations and delusions may warrant referral to a psychiatrist or neurologist for neuroleptic therapy.

5. Symptoms of depression are common in patients with AD. Depressed AD patients can develop behavioral changes (more irritability, agitation and wandering), as well as deterioration in self-care skills (Lyketsos et al, 1997). Suspicion of major depression in AD patients should warrant referral to a psychologist or psychiatrist for appropriate management.

D. PHARMACOLOGIC TREATMENT OF COGNITIVE DEFICITS

1. A cholinergic deficit has been demonstrated in parietal, temporal, and frontal lobes of patients in early stages of AD (Francis et al, 1999; Cummings and Black, 1998).

2. Level I evidence is available to support the modest symptomatic benefit of tacrine, donepezil, metrifonate and rivastigmine in treating patients with mild to moderate AD (Farlow et al, 1992; Rogers et al, 1996; Cummings et al, 1998; Francis et al, 1999). The latter two agents have not yet been approved by the FDA for marketing. These drugs do not prevent cell death or otherwise prevent the natural progression of AD.

3. Donepezil has three advantages over tacrine: a) fewer and less severe adverse effects, b) less risk of hepatotoxicity and c) a more convenient dosing schedule, allowing for better compliance (Rogers et al, 1996; Knopman and Morris, 1997).

4. Providers who have prescribing authority for donepezil and other drugs in this class should use the inclusion and exclusion criteria outlined in the VA Donepezil Reporting Form (Appendix I).

E. OTHER APPROACHES

1. There is level II evidence to suggest that vitamin E (alpha-tocopherol, a nonprescription drug), at a dose of 1000 IU p.o twice daily, delays the time to nursing home placement in moderately to severely impaired AD patients (Sano et al, 1997). It is not yet known whether this effect was a systemic one, or whether vitamin E was acting as a central antioxidant. High doses of vitamin E are contraindicated in patients with vitamin K deficiency or in those on anticoagulant drugs.

2. According to one randomized trial (level II evidence), a purified form of Ginkgo biloba was able to stabilize cognitive performance and social function for about a year in patients with mild to moderate AD (LeBars et al, 1997). Ginkgo biloba is an herbal remedy that currently lacks the production and safety standards of federally regulated pharmaceutical agents. Most adverse effects of Ginkgo biloba consist of mild gastrointestinal symptoms, but a few cases of serious bleeding have been reported (Ginkgo has antiplatelet effects).

3. Estrogen has been shown in one randomized trial (level II evidence) to enhance the cognitive benefit of tacrine in women with mild to moderate AD (Schneider et al, 1996). Yaffe and others (1998) reviewed the data suggesting that estrogen promotes cholinergic function in specific brain regions. Data from large randomized primary prevention trials are not yet available to know whether estrogen can safely and effectively delay the onset of AD in older women.

4. Doody (1997) has reviewed the evidence (level III) suggesting that nonsteriodal anti-inflammatory drugs (NSAIDS) delay the onset of symptoms in AD. Since these drugs are associated with significant risk (ulcers, hypertension, etc), they should not be routinely recommended for AD patients.

F. MONITORING & DISCONTINUATION OF CHOLINESTERASE INHIBITORS

1. Donepezil should be started at a dose of 5 mg p.o.daily. The family needs to be advised that this dose may not produce changes in cognition.

2. At 4-8 weeks, the dose of donepezil can be advanced to 10 mg p.o. daily, provided there are no serious side effects (nausea, anorexia, diarrhea, bradycardia, dizziness, or agitation).

3. Three to four months after initiating donepezil therapy, a visit needs to be scheduled to monitor the potential adverse effects of the 10 mg p.o. qd dose. At this point, the caregiver needs to tell the provider whether there have been any changes in memory, concentration, language fluency, or word recall. Benefit from donepezil at six months can be measured in some patients with the MMSE (Appendix III) or the FAQ (Appendix V).

4. Families need to understand that maintenance doses of donepezil may produce only modest symptomatic improvements in some AD patients. In others, the drug may only appear to stabilize the disease course, rather than to improve symptoms.

5. If the patient has lost weight because of anorexia or diarrhea, then the donepezil dose should be readjusted to 5 mg p.o. daily. This is also recommended if any other side effects develop, such as nausea or agitation.

6. If dosage reduction is ineffective in eliminating side effects, then donepezil should be discontinued.

7. Other reasons to discontinue donepezil include: a) poor compliance, b) no evidence of benefit after 6 months, c) mutual agreement between caregiver and provider, d) progression to severe dementia (MMSE <10), or e) development of a serious medical condition.

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Appendix I. VA Donepezil Reporting Form

Name: _____ Last 4 (SSN): _____ Date: _____
Age: _____ Education level (in years): _____
Facility: _____ Prescriber: _____

❑ This patient meets all of the following **DSM IV criteria for AD**:

_____ Loss of intellectual abilities sufficient to limit social or occupational functioning
_____ Memory impairment
_____ Impairment of either insight, judgement, executive function, language, or praxis
_____ Course has had gradual onset and progressive decline
_____ No clouding of consciousness, major depression, or schizophrenia
_____ No evidence of another cause of dementia, such as a brain tumor, subdural, hypothyroidism, B12 deficiency, tertiary syphilis, alcoholism, multi-infarct dementia or HIV encephalopathy

This is a community-dwelling AD patient with mild to moderate AD (MMSE ≥ 10) who has a caregiver to monitor drug compliance, efficacy, and adverse effects.

❑ This patient has none of the relative contraindications for use of donepezil:

- ❑ serious liver disease
- ❑ chronic alcoholism
- ❑ active peptic ulcer disease
- ❑ severe dementia
- ❑ bradycardia ≤ 50 beats/min
- ❑ severe COPD/asthma
- ❑ significant parkinsonism
- ❑ anticholinergic drugs

❑ The patient and caregiver understand that the common side effects of donepezil include nausea, bradycardia, diarrhea, anorexia, dizziness, and agitation/irritability. If surgery is needed, the surgeon should be informed about the drug's potential for interaction with succinylcholine.

❑ Follow-up contact at 4-8 weeks (to monitor potential adverse effects of the 5 mg p.o. qd dose of donepezil), and monitoring visits at 3-4 months (to observe possible benefit or adverse effects of the 10 mg p.o. qd dose) have been scheduled.

	MMSE Score	**Positive (+) or negative (-) effects (circle)**		
Baseline		Behavioral[a]	Motor[b]	Systemic[c]
4-8 weeks		+| - | none	+| - | none	+| - | none
3 – 4 months		+| - | none	+| - | none	+| - | none
6 – 9 months		+| - | none	+| - | none	+| - | none
Evidence from caregiver or MMSE that patient is at or above baseline?		Y or N	If "no", consider taper and D/C donepezil.	
Is patient still living at home?		Y or N	If "no", consider taper and D/C donepezil.	
Absence of behavioral, motor, or systemic adverse effects?		Y or N	If "no", consider taper and D/C donepezil.	

a = includes agitation, restlessness, and irritability
b = includes tremor, rigidity, bradykinesia, and gait disorder
c = includes nausea, diarrhea, bradycardia, and anorexia/weight loss

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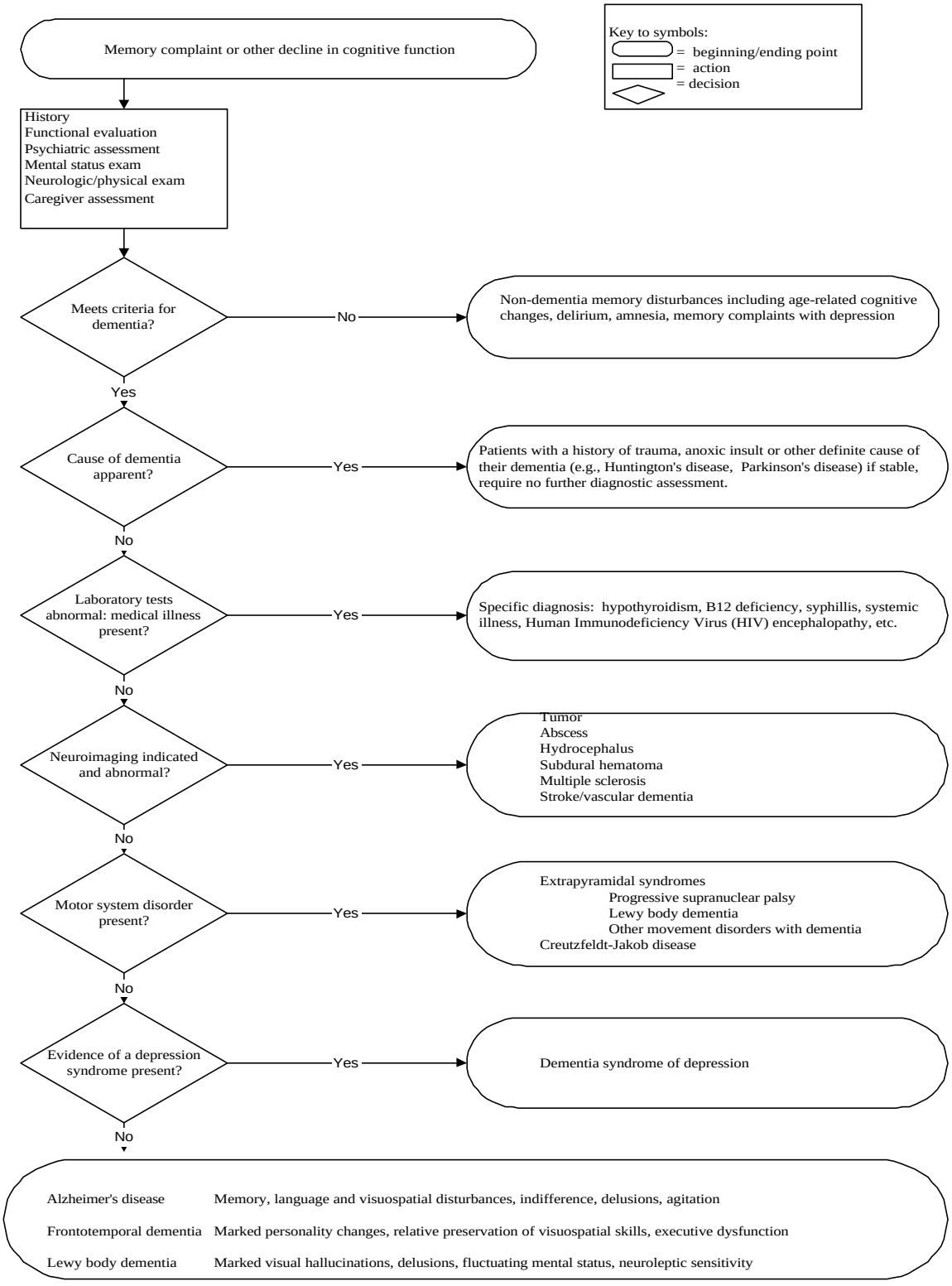
Appendix II. Algorithm Guiding the Differential Diagnosis of Dementia *



* From *Dementia Identification and Assessment: Guidelines for Primary Care Practitioners* U.S. Department of Veterans Affairs: Washington DC, and University Health System Consortium: Oakbrook, IL 1997.

Appendix III. Mini-Mental State Examination (MMSE) *

Name: _____
Date: _____ Last 4 (SSN): _____
Education: _____ Handedness:_____

1. What is today? Month? _____ Day? _____ Year? _____

   Day of Week? _____Season of Year? _____ _____ (5)

2. Where are we? City? _____ Country? _____ State? _____

   Name of hospital? _____ Floor? _____ _____ (5)

3. Repeat after me: ball - flag - tree

   Record the number recited initially. _____ (3)

   (Repeat them up to six times for adequate registration)

4. Subtract 7 from 100 (circle if correct): 93 - 86 - 79 - 72 - 65

   or spell WORLD forward and backward: D L R O W

   Write the greater of these two scores to the right: _____ (5)

5. Repeat the three words: ball - flag - tree _____ (3)

6. Read and obey: CLOSE YOUR EYES _____ (1)

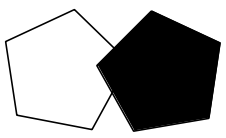
   Name these items (pen and watch) _____ (2)

   Repeat after me ("no ifs, ands, or buts") _____ (1)

   Take the piece of paper in your right hand, fold it in half, and put it on the floor _____ (3)

   Write a sentence: _____ _____ (1)

   Copy this design: _____ (1)



Total score _____ (30)

* adapted from J Psychiatry Res 12:189-198, 1975.

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Appendix IV. List of Anticholinergic Agents *

CLASS	AGENTS
Antidepressants	**Highest effects**: amitriptyline, amoxapine, clomipramine, protriptyline **Moderate effects**: bupropion, doxepin, imipramine, maprotiline, trimipramine **Minimal effects**: nortriptyline, desipramine, trazodone, phenelzine, paroxetine
Antiparkinson agents	benztropine, trihexyphenidyl
Antipsychotics	**Highest effects**: clozapine, mesoridazine, olanzapine, promazine, triflupromazine, thioridazine **Moderate effects**: chlorpromazine, chlorprothixene, pimozide **Minimal effects**: thiothixine, haloperidol, molindone, fluphenazine, trifluoperazine
Antispasmodics	atropine, belladonna alkaloids, dicyclomine HCl, glycopyrrolate, L-hyoscyamine, bromide, methscopolamine bromide, oxyphencyclimine HCl, propantheline bromide, tridihexethyl chloride, oxybutynin, flavoxalate, terodiline
Antihistamines	**Highest effects**: carbinoxamine, clemastine, diphenhydramine, promethazine **Moderate effects**: azatadine, brompheniramine, chlorpheniramine, cyproheptadine, dexchlorpheniramine, triprolidine, hydroxyzine
Antiemetic/Antivertigo agents	meclizine, scopolamine, dimenhydrinate, trimethobenzamide, prochlorperazine

* Includes non-prescription and prescription medications which have anticholinergic properties.

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Appendix V. Functional Activities Questionnaire *

Name: _____
Last 4 (SSN): _____Date: _____

Code: 0 = Normal function, or never did, but could.
1 = Difficult, but does alone; never did, but would be difficult to do alone.
2 = Requires assistance; never did, but would require assistance if attempted now.
3 = Totally dependent upon others to complete tasks.

1. Writing checks, paying bills, balancing checkbook: [ ]
2. Assembling tax records, making investments, etc: [ ]
3. Shopping alone for clothes, hardware, groceries: [ ]
4. Playing game of skill, working on a hobby: [ ]
5. Heating water for coffee, turning off stove: [ ]
6. Preparing balanced meal, setting the table: [ ]
7. Keeping track of current events, family events: [ ]
8. Paying attention to TV, reading the paper: [ ]
9. Remembering medications, appointments, etc: [ ]
10. Traveling out of neighborhood (car, taxi, bus): [ ]

Total: [ ]

* Adapted from J Gerontol 37: 323-329, 1982 (a score of 5 or more is consistent with a diagnosis of AD).

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Appendix VI. Barthel Index *

Name: _____
Last 4 (SSN): _____ Date: _____

_____ 1. Feeding: 10 = Independent if someone puts food within reach; finishes in time.
5 = Some help is needed in cutting food or in buttering bread.
0 = Totally dependent on others.

_____ 2. Transfers: 15 = Independent in all phases.
10 = Some help needed for safety.
5 = Needs to be lifted out of bed.
0 = Totally dependent on others.

_____ 3. Bathroom: 5 = Patient can wash/shave/brush teeth without assistance.
0 = Totally dependent on others.

_____ 4. Toilet: 10 = Independent in all phases.
5 = Some help needed with clothes/paper.
0 = Totally dependent on others.

_____ 5. Bathing: 5 = Independent in all phases
0 = Totally dependent on others.

_____ 6. Walking: 15 = Walks at minimum 50 yards (cane is permitted).
5 = Propels a wheelchair independently.
0 = Totally dependent on others.

_____ 7. Stairs: 10 = No help or supervision needed.
5 = Needs help carrying cane, etc.
0 = Totally dependent on others.

_____ 8. Dressing: 10 = Able to fasten clothing and tie shoes.
5 = Patient able to do ½ of the work.
0 = Totally dependent on others.

_____ 9. Bowels: 10 = No accidents.
5 = Has occasional accidents.
0 = Frequent fecal incontinence.

_____ 10. Bladder: 10 = No accidents; cares for Foley.
5 = Has occasional accidents, or needs help occasionally with Foley.
0 = Frequent urinary incontinence; usually requires diapers.

Total Score (100 maximum): _____

* Adapted from Md State Med J 14:61-65, 1995.

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Appendix VII. Clinical Dementia Rating *

Name: _____
Last 4 (SSN): _____ Date: _____

	Healthy (CDR 0)	Questionable Dementia (CDR 0.5)	Mild Dementia (CDR 1)	Moderate Dementia (CDR 2)	Severe Dementia (CDR 3)
Memory	No memory loss or slight inconsistent forgetfulness	Mild, consistent forgetfulness; partial recollection of events	Moderate memory loss that interferes with activities	Severe memory loss; only highly learned material retained	Severe memory loss; only fragments remain
Orientation	Fully oriented		Some difficulty with time relationships, may have geographic disorientation	Usually disoriented in time, often in place	Orientation to person only
Judgement, problem solving	Solves everyday problems well; judgement good	Only doubtful impairment in solving problems	Moderate difficulty with complex problems; social judgement maintained	Severely impaired in handling problems; social judgement usually impaired	Unable to make judgements or solve problems
Community affairs	Independent function in job, shopping, business and financial affairs	Only doubtful or mild impairment, if any in those activities	Unable to function independently in community	No pretense of independent function outside home	
Home + hobbies	Life at home, hobbies, intellectual interests well maintained	Life at home, hobbies, intellectual interests only slightly impaired	Mild impairment of function at home; chores difficult; hobbies abandoned	Only simple chores preserved; very restricted interests, poorly sustained	No significant function in home outside of own room
Personal	Fully capable of self-care		Needs occasional prompting	Requires assistance in dressing, hygiene, keeping of personal effects	Requires much help with personal care; often incontinent

* Adapted from Hughes CP, et al, Brit J Psychiatry 140:566".

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